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Chemistry Report
On Methyl Ethyl Ketone
EPCRA Section 313 Delisting Petition

by

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Economics, Exposure, and Technology Division
Office of Pollution prevention and Toxics

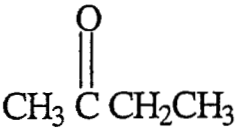
March 10, 1997

Methyl Ethyl Ketone (MEK)

- Chemistry Report -

Chemical Manufacturers Association Ketones Panel petitioned U. S. EPA to delist MEK to EPCRA section 313 list. MEK, next to acetone, is the most important commercially produced ketone. It is a clear, colorless, stable, low-boiling (not quite as volatile as acetone), and highly flammable liquid with acetone-like odor. It is very soluble in water (240 g/l at 20 °C), miscible with organic solvents, and forms azeotropes with water and many organic liquids. MEK has exceptionally high solvent power and is a good solvent for many natural and synthetic resins. It is used as a solvent (mainly in surface coatings) and chemical intermediate. MEK is subjected to volatile organic compound (VOC) regulations and is one of the seventeen chemicals in the EPA's 33/50 program subjected to voluntary emission reduction.

Chemical Name and Structure:



2-Butanone

CAS No.: 78-93-3

Synonyms (IPCS 1993): Butanone, 3-butanone, butane-2-one, ethyl methyl ketone, MEK, methyl acetone, methylpropanone, and others

Trade Names (TP 1992): MEETCO

Physical Properties:

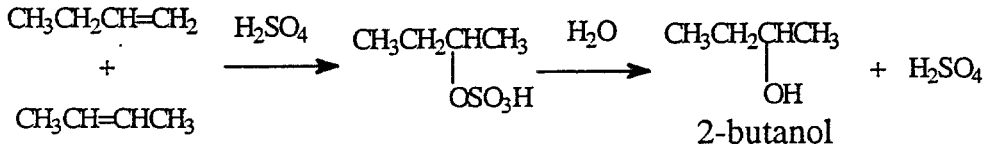
Appearance:	Colorless liquid with acetone-like odor
Molecular Formula:	C_4H_8O
Molecular Weight:	72.11
Density at 20 °C:	0.8054 (TP 1992)
Melting Point:	-86 °C (IPCS 1993)
Boiling Point:	79.6 °C (IPCS 1993)
Solubility:	
in water at 20 °C (g/l)	240, 268 (Kirk-Othmer, 3rd. Ed., Vol. 21 and 13 respectively), 263 (Exxon), 275 (IPCS 1993); decreases with increasing temperature.
in organic Solvents	Benzene, alcohol, ether, oils, most organic solvents (TP 1992)

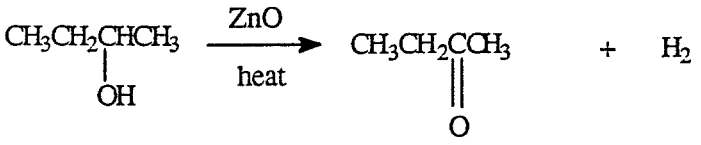
Solubility of water in MEK at 20 °C (g/l):	100 (Kirk-Othmer, 3rd. Ed., Vol. 21), 118 (Exxon)
Vapor Pressure at 25 °C (torr):	90.6 (TP 1992), 77.5 at 20 °C (IPCS 1993)
Log K_{ow}:	0.26 or 0.29 (IPCS 1993)
Log K_{oc}:	0.55 (TP 1992)
Henry's Law/Constant at 25 °C:	5.77 x 10^{-5} atm m^3/mol (TP 1992)
Bioconcentration Factor:	0.98 (calculated, TP 1992)
Autoignition Temperature:	515 °C (TP 1992)
Flash Point:	
Closed Cup	-2 °C (TP 1992)
Open Cup	1 °C (TP 1992)
Vapor Density (Air = 1):	2.41 (IPCS 1993)
Bulk Density at 20 °C:	6.71 lb/gal (Hawley's)
Relative Evaporation Rate:	
(n-Butyl Acetate = 100) at 20 °C	572 (Exxon)
Viscosity in Centipoise at 20 °C:	0.43 (Exxon)
Flammability Limits in Air:	2-10 % (TP-1992)
Saturation Concentration in Air:	301 g/m^3 at 20 °C (IPCS 1993)
Refractive Index:	1.3788 (IPCS 1993)
Conversion Factor:	1 ppm = 2.93 mg/ m^3 (TP 1992)
TLV-TWA (8 Hr.):	200 ppm (HSDB)

Chemical Properties (Kirk-Othmer, 3rd. Edition, Vol. 13, Ullmann's 1985, U.S. EPA 1985, and Exxon): MEK undergoes in chemical reactions typical of carbonyl group with activated hydrogen atoms adjacent to the carbonyl group, therefore it is a chemical intermediate for a variety of chemical products. The reactions include condensation, halogenation, ammonolysis, and oxidation. For example, MEK condenses with itself or aldehydes to form higher unsaturated ketones, reacts with ammonia and hydrogen to form secondary butyl amine, with acetylene to give methyl pentynol, a hypnotic compound, and with aliphatic esters, to produce 2,3-diketones. Direct oxidation of MEK (O_2/Cu_2 O) yields 2,3-butanediol (biacetyl), a valuable butter flavorer. With hydrogen peroxide MEK produces methyl ethyl ketone peroxide, an important initiator for polyester production. MEK is used in the preparation of rubber antioxidants and MEK oxime, an antiskinning agent in lacquers. MEK is not expect to undergo hydrolysis and oxidation in the environment, but when released into the atmosphere, it will degrade principally by reaction with photochemically produced hydroxyl radicals (HSDB, TP 1992, and IPCS 1993). Acetaldehyde is the primary product of this reaction (HSDB). MEK aborbs at approximately 240-320 nm region (U. S. EPA 1979). It would be expected to undergo some direct photolysis in the atmosphere; however, in water photodegradation is not expected to be significant (TP 1992). MEK is also readily degraded by microbes (U. S. EPA 1985). MEK vapor has narcotic effects (Ullmann's).

Manufacturing Processes (Kirk-Othmer, 3rd and 4th Editions and this petition): Most MEK is produced today by a two-step process starting from butenes, which is a mixture of 1-butene, 2-butene, butane, and isobutane (Kirk-Othmer, 4th Edition). The manufacture is in a

totally enclosed and continuous process. The first step is hydration of butene with sulfuric acid to give 2-butanol (both 1-butene and 2-butene give 2-butanol). 2-Butanol and co-products are stripped off and then 2-butanol is separated via distillation. Unreacted mixed butenes are sent to refinery for further processing and sulfuric acid is generately concentrated and recycled. The second step is vapor phased dehyrogenation of 2-butanol on zinc, copper, or bronze catalysts at high temperatures (400-500 ° C) and low pressures, similar to producing acetone from isopropanol. MEK is condensed and purified by distillation. Hydrogen is sold or burned. The yields are 90-95 mole % for each step.





MEK is also commercially available as a by-product from liquid phase oxidation of butane to acetic acid. Another process is direct oxidation of n-butenes using $PdCl_2$/2 CuCl.

Production Volume and Uses (Ullmann's 1985; Kirk-Othmer, 3 rd Edition; and Exxon Technical Product Bulletin): U. S. Production volume in 1994 was estimated at 545 million pounds (CPS). Two uses of MEK are solvent and chemical intermediate.

A. Solvent use: This use has been divided into catagories. The catagories according to Exxon Technical Product Bulletin are.

Surface coating -- MEK is mainly used in surface coating, typically in blends with other solvents for lacquers. It is fast evaporating and provides high solid content at low viscosity. MEK is widely used for vinyl lacquers such as vinyl acetate and vinyl chloride-vinyl acetate copolymers. It is also a strong solvent for nitrocellulose which is extensively used in furniture and automobile lacquers, for acrylic and acrylic-nitrocellulose lacquers, and for alkyds and other resins often used to modify nitrocellulose lacquers. MEK is widely used in surface coatings based on ethyl celullose, cellulose acetate-butyrate, polyurethanes, and vinyl chloride-acrylonitrile copolymer. Other uses for MEK are fabric and synthetic rubber coatings.

Adhesives -- MEK is a major solvent for solvent-based adhesives, paticularly rubber cements.

Magnetic tapes -- MEK is a solvent for the manufacture of magnetic tapes

Inks -- MEK is an important component in gavure printing ink and some of silk screen printing.

Solvent extraction -- MEK is used as an extraction solvent for fats, oils, waxes, and resins. It is also used as a processing solvent such as in pharmaceutical applications.

Traffic marking paint -- MEK is used as a solvent for traffic marking paint. Million of gallons of traffic marking paint are used every year. A lot of this paint is a solvent-based, oil modified alkyd resin type and some are fast dry paints formulated with chlorinated rubber.

Cleaning fluids -- MEK is widely used as paint, lacquer, and varnish removers as well as a cleaning fluid for industrial metals and engines.

Dewaxing agent -- MEK in mixture with benzene or toluene is used in petroleum refineries for reducing the wax content of lubricating oils.

Dyeing -- MEK is used as a solvent for various dyes and for inks used in printing on cellulose-derivative surface. Anthraquinone dyes for acetate fabric are prepared using MEK solvent. Oils and fats are removed from wool prior to dyeing by washing in MEK.

Miscellaneous -- MEK is a solvent for inseticides, fungicides, and germicides; various anti-oxidants; photographic film; artificial leather; in the manufacture of smokeless powder.

B. Chemical intermediate: MEK is also used as a chemical intermediate for manufacture of methyl isopropyl ketone and other higher ketones, flavorant, catalyst, antioxidants, perfumes, and etc. (see the Chemical Properties).

Exposure: . MEK is released mainly to the atmosphere from stack and fugitive emissions during its production, transport, use, and disposal. However, this chemical is not expected to persist in the environment or bioaccumulate in the food chain. MEK is present in the exhaust of automobiles (1 ppm), diesel engines, and jet aircraft as well as smoking cigarettes. MEK is also produced in small amounts by animals, higher plants, algae, and microbes. Low levels of MEK are also detected in a wide range of food such as bread, milk, meats, egg white, cottonseed oil, honey, coffee, cheese, potato chips, and beverages (TP 1992, IPCS 1993, and HSDB).

References:

CPS (Chemical Products Synopsis), Methyl Ethyl Ketone, Mannsville Chemical Products Corp, Adams, NY (1995).

Exxon Chemical Company MEK Technical Product Bulletin, Appendix B, this petition.

Hawley's Condensed Chemical Dictionary, 11th Edition, 1987, Van Nostrand Reihold Company, New York.

HSDB (Hazardous Substance Data Bank), CD-ROM (1995), SilverPlatter, from EPA Headquarter Library.

IPCS (International Programme on Chemical Safety), Environmental Health Criteria 143 on Methyl Ethyl Ketone, World Health Organization (1993).

Kirk-Othmer Encyclopedia of Chemical Technology, 3rd. Edition, Vol. 13 (1981), Vol. 21 (1983), and 4th Edition, Vol. 4 (1992), John Wiley Sons, New York.

TP (Toxicological Profile) for 2-Butanone, TP-91/08, July 1992, Agency for Toxic Substances and Disease Registry, Public Health Service, U. S. Department of Health & Human Services.

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U.S. EPA (U. S. Environmental Protection Agency), EPA/560/11-79-012, August 1979, Contract No. 68-01-41-09. Structure Reactivity Correlations for Environmental Reactions, Office of Technical Evaluation Office, Office of Toxic Substances, Washington, D. C.

U.S. EPA (U. S. Environmental Protection Agency), EPA/600/X-85/363, September 1985. Health and Environmental Effects Profile for Methyl Ethyl Ketone, Environmental Criteria and Assessment office, Office of Research and Development, Cincinnati, OH.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

E1-001

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JAN 22 1997

MEMORANDUM

SUBJECT: EPCRA Section 313 Delisting Petition: Absorption Review for Methyl Ethyl Ketone (MEK)

FROM: Leonard C. Keifer, Ph.D., FAIC 1-22-97
Chemist
Metabolism and Carcinogenesis Section
Health Effects Branch
Health and Environmental
Review Division (7403)

TO: Lorraine Randecker
Hazard Integrator
Analysis and Information Management Branch
Chemical Screening and Risk
Assessment Division (7402)

THRU: David Y. Lai, Ph.D. (1-22-97)
Acting Section Chief
Metabolism and
Carcinogenesis Section
Health Effects Branch
Health and Environmental
Review Division (7403)

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I. INTRODUCTION

A petition was filed for delisting MEK from Section 313 TRI reporting. At the request of the MEK work group a summary of the absorption of MEK from the lung and GI tract and through the skin is provided. The information presented is, for the most part, taken from the ATSDR toxicological profile for MEK (ATSDR, 1992).

II. CONCLUSIONS

MEK is well absorbed from the lung, GI tract, and skin. Pulmonary uptake in humans ranged from 41% to 56%. Case reports in humans and/or studies in rats demonstrate that MEK is absorbed from the GI tract and the skin; however, the available information was not sufficient to determine the percent of the dose absorbed.

III. BASES FOR CONCLUSIONS

A. Lung: 2-Butanone [MEK] is well absorbed during inhalation exposure. Pulmonary uptake in humans ranged from 41% to 56% of the inspired quantity (Liira et al. 1988a, 1988b, 1990 [all as cited in ATSDR, 1992]). Exercise increased the pulmonary uptake because of the greater ventilatory rate (Liira et al. 1988b [as cited in ATSDR, 1992]).

B. GI Tract: A woman who had metabolic acidosis after having accidentally ingested 2-butanone [MEK] stored in a rum bottle had a blood concentration of 95 mg/100 mL (13.2 mM) (Kopelman and Kalfayan 1983 [as cited in ATSDR, 1992]).

Oral administration (gavage) of 1,690 mg 2-butanone [MEK]/kg in rats resulted in a plasma concentration of 94 mg/100 mL at 4 hours (Dietz and Traiger 1979 [as cited in ATSDR, 1992]). Within 18 hours, the plasma concentration decreased to 6.2 mg/100 mL (Dietz and Traiger 1979 [as cited in ATSDR, 1992]).

These studies demonstrate that MEK is absorbed from the GI tract; however, the available information was not sufficient to determine the percent of the dose absorbed.

C. Skin: Measurable (2.54 to 13 μg/L) quantities of methyl ethyl ketone appeared in expired air of adult humans 3 min following dermal exposure to 100 mL of methyl ethyl ketone [MEK] applied to 91.5 cm^2 of skin (Wurster; J Pharm Sci 54: 554; 1965 [as cited in HSDB, 1997]). Data were not available to determine the percentage of the applied dose that was absorbed.

REFERENCES

ATSDR. 1992. Toxicological Profile for 2-Butanone [MEK]. U.S. Department of Health & Human Services. Public Health Section. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Mail Stop E-29, 1600 Clifton Road, N.E., Atlanta, GA 30333.

HSDB. 1997. Hazardous Substances Data Base Record for Methyl Ethyl Ketone.

cc: Fred Metz (7406)
Daniel Bushman (7408)

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

E1-002

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JUN 1 1997

MEMORANDUM

Subject: Hazard and Risk Assessment of Methyl Ethyl Ketone

From: Oscar Hernandez, Ph.D., Chief (Acting) O. Hernández
Existing Chemicals Assessment Branch
Risk Assessment Division (7403)

To: Maria Doa, Ph.D., Chief
Toxic Release Inventory Branch
Environmental Assistance Division (7408)

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Attached is the final hazard assessment of Methyl Ethyl Ketone (MEK), CAS No. 78-93-3, following RAD disposition of this chemical on May 21, 1997. The assessment conclusion is that, overall, there is low potential risk associated with exposure to MEK under the release scenarios described in the assessment.

All items discussed at disposition have been incorporated into this final version. These include the following:

- The estimated acute potential dose rates have been adjusted based on an average human female body weight of 65 kg, as provided by Mary Katherine Powers of EETD.
- The original study used to derive the IRIS RfC (Schwetz et al., 1991), was examined in order to determine the body weight of the adult mice tested. There was no indication of body weight and therefore the standard default of 25 g for mice was used in converting concentrations into dose equivalents. This body weight is consistent with that reported in other toxicity studies for the same strain (Swiss Albino) of mice.
- The use of an uncertainty factor of 100 for MEK to compare to the MOE was maintained.

- A caveat was added referring to the predicted level of concern for risk if a benchmark dose approach were used to analyze the developmental toxicity study results. This expectation is premised on the effects observed in the developmental study, which suggest that a benchmark dose assessment would lead to a higher non-detectable effect level than the one depicted by the experimentally determined NOAEL.

Attachment

HAZARD ASSESSMENT OF METHYL ETHYL KETONE

(In response to Section 313 delisting petition of
the Chemical Manufacturers Association, Arlington, VA)

1. BACKGROUND

On November 29, 1996, the Chemical Manufacturers Association (CMA) repetitioned the Agency to delete **methyl ethyl ketone (MEK)** from the list of chemicals subject to the reporting requirements of Section 313 of the Emergency Planning and Community Right-To-Know Act of 1986. CMA had submitted a petition to delete **MEK and methyl isobutyl ketone** from Section 313 in September 1988, but this petition was withdrawn based on the Agency's concerns for developmental toxicity and neurotoxicity. Since that time, as a result of new information or a reevaluation of existing information, the level of concern for these effects has decreased (IRIS 1993). This is CMA's basis for resubmitting the petition.

MEK ($CH_3COCH_2CH_3$) is a clear, colorless, organic liquid with a sharp sweet odor. It is miscible with water and a variety of organic solvents. Its greatest use is as a solvent in the surface coatings industry, specifically vinyl lacquers, nitrocellulose lacquers, and acrylics. It is also used as a solvent for adhesives, printing inks, degreasing and cleaning fluids, smokeless powder, and the hard wood pulping industry and as an intermediate in the production of antioxidants, perfumes, and catalysts.

Currently, MEK is produced in the US by three companies: Exxon Chemical CO., Hoechst Celanese, and Shell Chemical. Estimated total domestic capacity in 1995 was ca. 595 million pounds.

In humans, inhalation of high doses produces irritation of the eyes and upper and lower respiratory system, effects characteristic of solvent exposure. (USEPA(b), HE RD memorandum dated January 30, 1997). Likewise, animal data indicates that MEK has toxic effects only at high doses. For example, in acute oral toxicity studies, the LD_{50} in rats and mice ranges from 2.5-5.6 g/kg and in subchronic inhalation studies, decreases in body weight, increases in liver weight and liver weight to body weight ratios, and increases in enzyme activity, were observed only at high doses (5,000 ppm) (IRIS 1993). The NOAEL and LOAEL were 1,010 and 3,020 ppm, respectively, based on the developmental study used to derive the IRIS RfC(IRIS, 1993). The **RfC for MEK is 1.0 mg/m^3**, or ca. 0.3 ppm. The OSHA PEL for MEK is 200 ppm, or ca. 589 mg/m^3. Because of the low hazard (low intrinsic toxicity) for MEK, the Environmental Assessment Division (EAD) requested that the Risk Assessment

Division (RAD) perform a risk assessment.

2. HAZARD SUMMARY

2.1 Absorption and Metabolism

MEK is well-absorbed from the lung, GI tract, and skin. Pulmonary uptake in humans ranged from 41% to 56%. (USEPA(a), HERD memorandum dated January 22, 1997).

2.2 Acute Toxicity

Available data indicate that MEK has low acute toxicity. In humans, inhalation of high doses produces irritation of the eyes and upper and lower respiratory system, effects characteristic of solvent exposure. (USEPA(b), HERD memorandum dated January 30, 1997). In acute oral toxicity studies, the LD_{50} in rats and mice ranges from 2.5-5.6 g/kg.

2.3 Carcinogenicity

MEK is classified in IRIS as D, not classifiable as to human carcinogenicity, based on no human carcinogenicity data and inadequate animal data. (IRIS, 1993).

2.4 Mutagenicity

MEK was negative in the Ames assay with and without activation. It induced chromosome mutations (aneuploidy) in yeast cells. It also induced cell transformation in BALB/c cells. It was also negative in the following: in the UDS assay, for SCE's in CHO cells, in the mouse micronucleus assay, for gene mutations in E. coli, in the mouse lymphoma assay, and for chromosome aberrations in CHO cells. (USEPA(c), HERD memorandum dated January 24, 1989).

2.5 Systemic Toxicity from Repeated Doses

Available data indicate that MEK appears to have low systemic toxicity and is, therefore, of low health concern. Although no chronic studies have been found, several well-designed repeated-dose oral and inhalation studies in laboratory animals demonstrate low systemic toxicity with MEK (USEPA(b), HERD memorandum dated January 30, 1997). For example, in subchronic inhalation studies, decreases in body weight, increases in liver weight and liver weight to body weight ratios, and increases in

enzyme activity, were observed only at high doses (5,000 ppm) (IRIS 1993).

2.6 Developmental Toxicity

☐ The key study, on which the RfC is based, is an inhalation developmental toxicity study in Swiss **mice** (Schwetz et al. 1991, as cited in attached assessment). This study was not available at the time of the first petition. Four groups of 10 virgin and 33 pregnant mice were exposed to 0, 398, 1,010, or 3,020 ppm (0, 1,174, 2,978, or 8,906 mg/m^3) MEK 7 hr/day during gestation days 6-15.

Neither maternal nor developmental toxicity were observed at the low or mid doses. At 3,020 ppm, there was a decrease in fetal body weight that was significant only in males and a significant trend in the incidence of misaligned sternebrae when measured on a fetus but not litter basis. At this dose there was also an increase in maternal relative liver and kidney weight, but the biological significance of this effect is not known (IRIS 1993).

☐ Based on the dose level at which these effects were observed, the concern for developmental toxicity appears to be low. The **LOAEL is 3,020 ppm** and the **NOAEL is 1,010 ppm.**

☐ The two inhalation studies that formed the basis of concern for the first petition were conducted in **rats** by the same group of researchers and in the same laboratory. In the first study (Schwetz et al. 1974, as cited in IRIS 1993), animals were exposed to 0, 1,126, or 2,618 ppm (0, 3,320, or 7,720 mg/m^3). At the low dose, there was a decrease in fetal body weight and crown:rump length; these effects were not seen at the high dose. There was also a significant increase in total number of litters containing fetuses with skeletal anomalies. At the high dose, there was a significant increase in number of fetuses and litters having gross anomalies. Maternal toxicity was not observed. The apparent **LOAEL is 1,126 ppm.**

The second study (Deacon et al. 1981, as cited in the IRIS 1993) was conducted to determine the repeatability of the above findings. Exposures were to 0, 412, 1,002, or 3,005 ppm (0, 1,215, 2,955, or 8,861 mg/m^3). No effects were seen at the low or mid dose. At the high dose, there was delayed ossification of bones in the skull and cervical centra and an increase in the incidence of extralumbar ribs. There was also decreased maternal body weight gain and increased water consumption at the high dose. The apparent **NOAEL is 1,002 ppm,** and the **LOAEL is 3,005 ppm.**

2.7 Reproductive Toxicity

▣ Data on MEK could not be found. There is a two-generation rat study with **2-butanol** (a metabolic precursor to MEK) in which Wistar rats (30/sex/group) were given 0, 0.3%, 1.0%, or 3.0% in drinking water. Because of significant toxicity seen in the high-dose group, treatment of high-dose parents and offspring was reduced to 2.0%. The critical effect was **decreased fetal birth weight** at the 2.0% dose. Based on the dose level at which these effects were observed, the concern for reproductive toxicity appears to be low. The **LOAEL for 2-butanol is 2.0% (3,122 mg/kg/day)** and the **NOAEL is 1.0% (1,771 mg/kg/day).** (USEPA(b), HERD memorandum dated January 30, 1997).

2.8 Neurotoxicity

▣ According to the latest IRIS report on MEK, which was updated 6/93, "at present, there is no convincing experimental evidence that MEK is neurotoxic in either experimental animals or humans other than possibly inducing CNS depression at high exposure levels." Prior concerns were based on enhancement by MEK of neurotoxicity seen with other solvents.

2.9 Environmental Effects

▣ MEK is of low concern with respect to aquatic toxicity based on measured toxicity data and SAR analysis. The fish 96-hr LC50 values range from 2,300 to 3,220 ppm; the daphnid 48-hr LC50 values range from 2,200 to 5,091 ppm, and the green algal 96-hr EC50 is 1,200 ppm. The fish chronic values range from 220 to 300 ppm, the daphnid chronic value is 52 ppm, and the algal chronic value is 45 ppm. In addition, the bioconcentration factor is low, 0.640. (USEPA(d), HERD memorandum dated December 10, 1997).

3. EXPOSURE SUMMARY (USEPA(e), EETD memorandum dated January 28, 1997)

Most of the industrial releases of MEK are to **air**. According to the SIDS Initial Assessment Report [USEPA(f) 1995], the concentrations of MEK in the environment are low, because MEK is manufactured in totally enclosed continuous processes, and significant emission reductions have been made over the past few years. The SIDS Report, however, did not present monitoring data for MEK levels at the fenceline of MEK facilities.

In addition, the Ketones panel had submitted an exposure report for MEK performed by ENSR Corporation as part of the petition for delisting. It appears that an extensive amount of work has been done (in many cases using EPA models). However, insufficient site-specific information was included for an adequate evaluation

of their results. In addition, some debatable assumptions were made, such as the statement that "airborne concentrations are likely to be highest around facilities with the highest emission rates". This is not necessarily true. Airborne concentrations depend on weather conditions as well as emission rates. For these reasons, exposure estimates based on the concentrations in air presented in the petition are not included in this report.

Concentrations and exposures resulting from the fugitive and stack air releases in the TRIS download were estimated using equations developed based on PTPLU, a single source Gaussian dispersion algorithm. The PTPLU model provides ground-level concentrations which are hourly average values.

The scenarios modeled assume that there is no treatment of these stack and fugitive releases, and therefore no reduction in the amount released to the environment. These concentrations can be expected to occur up to 250 meters from the source, which may be beyond the facility fenceline.

Estimated concentrations are based on the assumption that releases take place continuously over 365 days per year; releases occurring over shorter periods will result in higher concentrations. This will be true no matter what short-term model is employed. There is no way to determine the number of release days from reports to the TRIS database. It is safe to assume, however, that acute estimated concentrations can occur at points beyond facility fencelines.

A combination of both conservative and non-conservative assumptions were used to generate these equations. The conservative assumptions include the use of weather station data known to generate the highest concentrations and therefore potential exposures, as well as a 24-hour exposure duration. Non-conservative assumptions include the assumption that TRI releases are spread over 365 days per year, 24 hours a day, and a 24-hour averaging time for concentration estimates. Given a shorter release period, estimated exposures could be significantly higher.[1]

This procedure generates estimates of concentrations and exposures under three different scenarios including a variety of wind conditions, including relatively stagnant situations. These three scenarios have been labeled 1) the typical scenario, 2) the stagnation scenario, and 3) the maximum scenario. The model does not consider decay of the chemical in the environment.

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[1]Some short-term concentrations are outside the scope of PTPLU, due to either release fluctuations, geography, or combinations of source geometry and atmospheric conditions. Concentrations with durations of several minutes can significantly exceed hourly averages modeled here.

The environmental assumptions applied to each scenario are summarized below. The wind speeds for the scenarios occur at a height of ten meters, and the runs used wind speeds varying with height.

Typical scenario: wind speed of five meters per second, and a 24-hour duration.

Stagnation scenario: wind speed of 2 meters per second, and a 24-hour duration. It was designed to model an outdoor stagnation episode exceeding 24 hours. This scenario does **not** mean closed-room conditions; it is a relative term to indicate calm outdoor conditions with low wind dilution.

Maximum scenario: wind speed of 0.5 meters per second, and a two-hour duration. It models the least air dilution during stagnant conditions.

Using PTPLU, concentrations were modeled at 50-meter intervals beginning at 50 meters downwind from the source. Model output reported results across stability classes for a range of wind speeds effective at the stack top. The runs used wind speeds varying with height.

The assumptions used in estimating acute potential dose rates (APDRs) are as follows:

Typical: An inhalation rate of 11.3 m^3/day, a body weight of 65 kg[2], and a twenty-four-hour averaging period.

Stagnation: An inhalation rate of 11.3 m^3/day, a body weight of 65 kg, and a twenty-four-hour averaging period.

Maximum: An inhalation rate of 0.47 m^3/hr, a body weight of 65 kg, and a two-hour averaging period.

The inhalation rates and body weights cited above are average values for adult females. Data for pregnant women as a group are not available. An inhalation rate of 0.47 m^3/hr was used in the maximum scenario. This value was generated by dividing the daily inhalation rate of 11.3 m^3 by 24 hours.

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[2]The female average body weight is based on a mean value for adults age 18-75 of 65.4 kg based on a single study cited in the Department of Health and Human Services Publication No. (PHS) 87-1688.

Estimated concentrations in air and APDRs resulting from stack releases are shown in Table 1. Estimated concentrations and APDRs resulting from fugitive releases are shown in Table 2.

Due to a lack of more specific information, these exposure estimates are based on "what-if" scenarios. A "what-if" scenario is defined by EPA's 1992 Exposure Assessment Guidelines as one which answers the question, "What potential dose rates result if the following exposure conditions are assumed?" Assumptions are then made about representative conditions. Please note that a "what-if" scenario contains no estimate of the probability of the estimated exposures.

TABLE 1
ACUTE EXPOSURES RESULTING FROM STACK RELEASES

Discharging Facility	Amount Released (lb/yr)	Ambient Concentration (mg/m^3)			Estimated APDRs (mg/kg/day)		
		Typical	Stagnant	Maximum	Typical	Stagnant	Maximum
Gencorp	1,722,746	9	17	103	2	3	1
O'Sullivan Corp.	1,365,329	6	14	82	1	2	1
IPC Corinth Div. Inc.	1,168,782	6	12	70	1	2	1
Resilite Sports Products, Inc.	648,757	3	6	39	0.5	1	0.5
3M Middleway Plant	615,500	3	6	37	0.5	1	0.5

TABLE 2
ACUTE EXPOSURES RESULTING FROM FUGITIVE RELEASES

Discharging Facility	Amount Released (lb/yr)	Ambient Concentration (mg/m^3)			Estimated APDRs (mg/kg/day)		
		Typical	Stagnant	Maximum	Typical	Stagnant	Maximum
Mobil Oil Beaumont Refinery	1,200,000	12	110	240	2	20	3
Texas Recreation Corp.	790,100	8	70	160	1	10	2
Sun Refining and Marketing	640,000	6	60	130	1	10	2
Shell Oil Deer Park Manufacturing Complex	508,017	5	50	100	1	8	1
Amoco Oil Co. Whiting Refinery	480,000	5	40	100	1	7	1

Typical scenario: wind speed of five meters per second, and a 24-hour duration.

Stagnation scenario: wind speed of 2 meters per second, and a 24-hour duration. It was designed to model an outdoor stagnation episode exceeding 24 hours. **Note:** this does **not** mean closed-room conditions; it is a relative term to indicate calm outdoor conditions.

Maximum scenario: wind speed of 0.5 meters per second, and a two-hour duration. It models the least air dilution during stagnant conditions.

NOTE: The "maximum" scenario is anticipated to last for only two hours, as compared with the 24-hour duration of the "typical" and "stagnation" scenarios. This means that while the "maximum" concentrations will always be the highest, the "maximum" exposures do not exceed the "stagnation" exposures.

4. RISK ASSESSMENT

This assessment focuses on the potential risk associated with estimated exposures to MEK at or beyond the facility site boundary. The exposure estimates illustrated in this assessment utilize release information submitted under TRI and standard modeling techniques to derive ambient air concentrations of MEK under three release scenarios (typical, stagnant, and maximum or peak) for the top releasing facilities in each category - stack and fugitive- of air emissions.

The IRIS **RfC of 1.0 mg/m^3** for MEK is based on mild, but significant developmental toxicity (decreased fetal body weight and misaligned sternebrae) at 3,030 ppm in the inhalation developmental toxicity study in mice (Schwetz et al. 1991, as cited in IRIS 1993).[3] An RfC by definition represents an "estimate (with uncertainty spanning an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime". As such, the RfC incorporates adjustments to account for uncertainties about portal of entry and long-term exposure effects. Because of emphasis on developmental effects, it would not be appropriate to use the RfC for assessing the potential risk of developmental toxicity associated with acute exposure to MEK. It would be more appropriate to derive a RfC_{DT} and compare it with the estimated human exposure concentration. There is, however, no official Agency RfC_{DT}. Instead, a margin of exposure (MOE)[4] approach was used. The rationale for following this approach was that the effect of concern for MEK is developmental toxicity, which requires assessment of short-term exposures.

Most releases of MEK are to air; thus, only airborne exposures were considered. Furthermore, because the critical effect is developmental toxicity, which can be initiated upon acute exposure, **acute ambient concentrations** estimated by the Point Plume (PTPLU) model were the exposure concentrations selected.

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[3]The RfC was set with an uncertainty factor of 1000: 10 for interspecies extrapolation, 10 for sensitive individuals, and 10 for incomplete database including a lack of chronic and reproductive toxicity studies; and with a modifying factor of 3 for lack of unequivocal data for the respiratory tract (portal-of-entry) effects, for a total adjustment factor of 3000. Confidence in the RfC is low due to medium confidence in the principal study and low confidence in the database. (IRIS, 1993). Furthermore, developmental effects in rats were not consistent between studies.

[4]The MOE is the ratio of the NOAEL of the critical toxic effect to the estimated human exposure levels. When the MOE is equal or greater than the product of applicable uncertainty and modifying factors (see footnote 1), the chemical is likely to be of low concern. For MEK, this uncertainty factor is 100.

Table 3: Acute MOE Calculations for Stack Releases[a]

Discharging Facility	Typical	Stagnant	Maximum
Gencorp	690	460	1380
O'Sullivan Corp.	1380	690	1380
IPC Corinth Div. Inc.	1380	690	1380
Resilite Sports Products, Inc.	2760	1380	2760
3M Middleway Plant	2760	1380	2760

[a]The MOE is the ratio of the NOAEL in the mouse developmental study (1380 mg/kg/day) to APDR estimates in Table 1.

Table 4: Acute MOE Calculations for Fugitive Releases[a]

Discharging Facility	Typical	Stagnant	Maximum
Mobile Oil Beaumont	690	69	460
Texas Recreation Corp.	1380	138	690
Sun Refining and Marketing	1380	138	690
Shell Oil Deer Park Manufacturing Complex	1380	172	1380
Amoco Oil Co. Whiting Refinery	1380	197	1380

[a]The MOE is the ratio of the NOAEL in the mouse developmental study (1380 mg/kg/day) to APDR estimates in Table 2.

MOE calculations for acute ambient exposures for stack and fugitive releases from the top ten discharging facilities are summarized in Tables 3 and 4. In each case, the NOAEL (ca 1380 mg/kg/day)[5] from the mouse developmental toxicity study was divided by the acute estimated average potential dose rates (APDRs). The default assumptions for the mouse ventilation rate and mouse body weight were based on values given in USEPA (g). These appear to be consistent with the strain of mouse (Swiss Albino) tested in the developmental toxicity study by Schwetz, et al. (1991).

As can be seen in Tables 3 and 4, the MOE is greater than 100 for stack releases under all three exposure scenarios; typical, stagnant, and maximum (peak). For

[5]ppm → mg/kg/day = [ppm x (molecular weight/24.5) x mouse ventilation rate (m^3/day) x duration of exposure (hr/day) ÷ mouse body weight (kg) = mg/kg/day
[1010 ppm x (72.1/24.5) x 0.040 m^3/day x 7 hr/24 hours] ÷ 0.025 kg = 1380 mg/kg/day

fugitive releases, the MOE is greater than 100 for all three exposure scenarios, except one discharging facility under stagnant scenarios.

Conclusions

Overall, the assessment supports low potential risk for developmental effects to individuals exposed to MEK. This conclusion is based on MOE values greater than 100 for the top releasing facilities with one exception. A potential risk is indicated by an MOE value lower than 100 for one facility under exposure conditions characterized by fugitive releases under a stagnant scenario. It should be noted that the exposure estimates are based on facility release estimates, which generally are not the result of monitoring studies. Also, the APDRs assume that the target population is exposed to ambient (outdoor) air continuously. Thus, the risk characterization reflects potential concerns engendered by estimated high exposures. The hazard assessment strongly indicates that MEK has low acute and chronic (systemic) toxicity in that effects occur only at high doses. Specifically, developmental toxicity for MEK is characterized by high dose effects and lack of consistency between studies for one species. Furthermore, based on the developmental effects observed, if the MOE were calculated on the basis of a benchmark dose instead of the apparent NOAEL from the developmental toxicity study, the concern for potential risk would be further weakened, if not eliminated. Therefore, under the exposure conditions described here there appears to be low potential risk associated with exposure to MEK.

6. REFERENCES

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Delisting Petition. Memorandum dated January 28, 1997, from Mary Katherine Powers, EETD. Washington, DC:USEPA.

USEPA(f). 1995. OECD-SIDS: Review of US Initial Assessment Reports. Methyl ethyl ketone. Memorandum dated April 30, 1995, from Oscar Hernandez, Chief, Risk Analysis Branch, CSRAD, to Angela Auletta, Chief, Health Effects Branch, HERD. Washington, DC: USEPA.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OCT 6 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Review of the Interactive Effects of Methyl Ethyl Ketone (MEK) with Neurotoxic Solvents: Response to OSHA/NIOSH Comments

From: Lois Dicker, Ph.D., Chief
Existing Chemicals Assessment Branch
Risk Assessment Division (7403)

To: Maria Doa, Ph.D., Chief
Toxic Release Inventory Branch
Environmental Assistance Division (7408)

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Per your request (memorandum dated September 4, 1997), RAD has reviewed the letters, references, and other materials sent to EAD by NIOSH and OSHA concerning the interactive effects of MEK with neurotoxic solvents (RAD reviews attached). Epidemiological data involving acute exposures at low doses report no adverse effects related to co-exposure of MEK with MIBK, toluene, or acetone. There were no epidemiological data involving chronic exposures. Animal studies indicate that MEK alone produces only transient neurological effects at high vapor concentrations with no evidence of permanent damage to the nervous system. However, MEK in the presence of other neurotoxic solvents such as, n-hexane and methyl-n-butyl ketone, appears to potentiate neurotoxicity.

While the animal data support the potentiation of the neurotoxicity of other solvents by MEK, the data are inadequate to fully characterize the mechanism of action. While it is prudent to consider the potentiation of MEK in the workplace setting as pointed out by OSHA and NIOSH, RAD does not believe an accurate evaluation of effects due to MEK potentiation is possible under the TRI statute at this time. Lack of information

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concerning human exposure scenarios and the composition of chemical mixtures at facility fencelines, as well as lack of information on the mechanism of action of MEK with other solvents all contribute to this.

We will however, in the future discuss when appropriate, the possibility of synergistic effects of a chemical in RAD hazard/risk assessments prepared for TRI listing/delisting requests.

Attachments (2)

cc: Vanessa Vu
Oscar Hernandez
Andrea Pfahles-Hutchens
Deborah Norris
Katherine Anitole
Dan Bushman (7408)
Carol Christensen (7408)

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

E1-004

3PP

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

12-10-96

MEMORANDUM

SUBJECT: Delisting Petition for Methyl Ethyl Ketone: Environmental Toxicity

FROM: J. V. Nabholz, Ph.D.
Health and Environmental
Review Division (7403)

TO: Daniel R. Bushman
Acting Petitions Coordinator
ET501B, 202-260-3882
Environmental Assistance Division (7408)

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I have reviewed the delisting petition for methyl ethyl ketone (MEK) [78-93-3]. MEK is of low concern with respect to environmental toxicity based on known measured toxicity data and structure activity relationship (SAR) analysis.

1. TOXICITY PROFILE: The toxicity profile for methyl ethyl ketone is:

methyl ethyl ketone **[78-93-3]**
MEK; 2-butanone; methyl acetone; smiles: CCC(=O)C; MW72; liquid; log K_{ow} = 0.26 (CLOGP), 0.26 (SRC), 0.29 (M-Hansch&Leo 1958); water solubility = 24 g/L (M-ICB), 275.0 g/L (Merck), 95.3 g/L (M-SRC), 263 g/L @ 20 °C (M-Exxon-SIDS); vp = 77.5 mm Hg @ 20 °C (M-ICB, DeLP), 100 mm Hg @ 25 °C (HC&P-CRC); and HLC = 5.6E-5 atm.m^3/mol (P-EAB), 3.98E-1 atm.m^3/mol (P-SIDS), 1.05E-5 atm.m^3/mol (DeLP).

RM1; OECD SIDS; SARA Sec. 313 TRI; Lead encapsulant chemical;

Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:

fish 96-h LC50	=	2300.0	P
fish (FHM) 96-h LC50	=	3220.0	M FT,M ERL-Dul
fish (SHM) 96-h NOEC	=	400.0	M S,N Heit81 FLAG
daphnid 48-h LC50	=	**2200.0**	**P**
daphnid 48-h LC50	=	5091.0	M S,N R&K80 FLAG

green algal 96-h EC50	=	1200.0	P
green algal 192-h EC50	=	4300.0	M S,N B&K78 FLAG
fish Chronic Value (ChV)	=	220.0	P
fish ChV	=	300.0	P ACR10
daphnid ChV =		52.0	P
algal ChV =		45.0	P

Biological Fate

fish BCF	=	0.640 P

low concern for toxicity based on SAR;
low concern for toxicity based on known test data;

assessment factor (AsF)	=	10.0
CC (fish)	=	30.0
CC (daphnids)	=	5.0
CC (green algae)	=	5.0

low concern for bioconcentration potential in aquatic organisms based on SAR;

FLAG = Static method with nominal concentrations in open test systems, i.e., B&K78 used an open test tube over 8 days; beware of loss of MEK via volatilization.

Abbreviations are:

ACR10 = acute-to-chronic ratio = 10;
ai = active ingredients;
AsF = assessment factor;
BCF = bioconcentration factor;
CC = concern concentration;
ChV = Chronic value;
DeLP = delisting petition;
EC = effective concentration;
M = measured concentrations;
N = nominal concentrations;
NOEC = no-observed-effect concentration;
S = static method;
SAR = structure activity relationship;
TOC = total organic carbon;

Prediction were based on SARs for neutral organic chemicals; MW72; log K_{ow} = 0.26 (CLOGP); pH = 7; hardness <180.0 mg/L as $CaCO_3$; effective concentrations based on 100% active ingredients and mean measured concentrations; and TOC <2.0 mg/L;

References:

B&K78 = Bringmann & Kuhn (1978, Mitt. Int. Ver. Theor. Angew. Limnol. 21:275-284).

ERL-Dul = Tested at the Unites States Environmental Research Laboratory-Duluth, Office of Research and Development, Environmental Protection Agency on 15 May 1980 and published in Brooke et al (1984, Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), University of Wisconsin-Superior, p.99; and in Veith et al (1983, Aquatic toxicity and hazard assessment, 6th Symp., ASTM STP802, Philadelphia, PA, p.90-97).

HC&P = Handbook of Chemistry and Physics, Chemical Rubber Company.

Heit81 = Heitmuller et al (1981, ...)

R&K80 = Randall & Knopp, 1980, J. Water Pollut. Contr. Fed. 52(8):2117-2130.

2. QUESTIONS: If you have any further questions, please call (202-260-1271), fax (202-260-1236 or -1283), LAN mail, email: nabholz.joe@epamail.epa.gov; or visit (E427).

21 YELLOW

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Delisting Petitions for Methyl Ethyl Ketone (MEK) and Methyl Isobutyl Ketone (MIBK): Mutagenicity Hazard

FROM: Michael C. Cimino, Ph.D.
Biologist
Toxic Effects Section
Toxic Effects Branch
Health and Environmental
Review Division (TS-796)

11/7/84

TO: Elbert Dage
Chemical Manager
Chemical Review and Evaluation Branch
Health and Environmental
Review Division (TS-796)

THRU: Angela Auletta, Ph.D.
Section Chief
Toxic Effects Section
Toxic Effects Branch
Health and Environmental
Review Division (TS-796)

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I. SUMMARY

The two delisting petitions slightly underrepresent the mutagenicity hazard presented by methyl ethyl ketone (MEK) and methyl isobutyl ketone (MIBK). Although MEK shows little evidence of mutagenicity, it does induce cell transformation in mammalian cells in culture. MIBK shows slightly greater evidence of mutagenicity, with a weak positive response in mammalian cells in culture. It also induces cell transformation in mammalian cells in culture.

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II. DISCUSSION

A. MEK

A HERD review of the TSCA Section 4 mutagenicity data on methyl ethyl ketone (MEK: Cimino 1985) disagrees with one of the conclusions in the delisting petition. HERD assesses the cell transformation assay as positive, based upon review of the same industry data referred to in the petition (p.23). The delisting petition cites a manuscript by O'Donoghue et al. which deals with these same industry data. (This manuscript has recently been published; O'Donoghue et al. 1988.) After re-evaluating the HERD review in light of the O'Donoghue paper, no convincing arguments have been presented to change HERD's conclusions.

Three other papers cited by the petition have been reviewed (Brooks et al. 1988; Perocco et al 1983; Zimmermann et al 1985). HERD concurs with the data evaluation on these papers.

SUMMARY OF MUTAGENICITY DATA ON MEK

Gene mutations:	Negative Salmonella/Ames
	Negative Escherichia
	Negative lymphoma
Chromosome mutations:	Positive Saccharomyces aneuploidy
	Negative CHO cells in vitro
	Negative RL4 cells in vitro
	Negative mouse micronucleus in vivo
DNA effects:	Negative Saccharomyces recombination
	Negative sister chromatid exchange in CHO cells in vitro
	Negative rat hepatocyte UDS
	Negative DNA synthesis in human cells in vitro
Cell transformation:	Positive BALB/c mouse cells in vitro

There are no animal data indicating that MEK may induce heritable mutations.

B. MIBK

A HERD review of the TSCA Section 4 mutagenicity data on methyl isobutyl ketone (MIBK: Cimino 1985) disagrees with some of the conclusions in the delisting petition. The mouse lymphoma assay is assessed as being a positive response (albeit weak), and the cell transformation assay is assessed as positive. These assessments are based upon review of the same industry data referred to in the petition (pp.23-28). As stated above for MEK, re-consideration of these data in light of the O'Donoghue et al. paper does not change HERD's conclusions.

The OHEA document on MIBK (OHEA 1986, p.11) suffers from the same deficiencies in interpretation for the lymphoma and cell transformation assays as the delisting petition.

Another paper cited by the petition has been reviewed (Brooks et al. 1988). HERD concurs with the data evaluation on this paper.

SUMMARY OF MUTAGENICITY DATA ON MIBK

Gene mutations:	Negative Salmonella/Ames
	Negative Escherichia
	Positive lymphoma
Chromosome mutations:	Negative CHO cells in vitro
	Negative RL4 cells in vitro
	Negative mouse micronucleus in vivo
DNA effects:	Negative Saccharomyces recombination
	Negative rat hepatocyte UDS
Cell transformation:	Positive BALB/c mouse cells in vitro

There are no animal data indicating that MIBK may induce heritable mutations.

III. CONCLUSIONS

The two delisting petitions slightly underrepresent the mutagenicity hazard presented by MEK and MIBK. MEK shows little evidence of mutagenicity. However, it induces cell transformation in mammalian cells in culture. MIBK shows slightly greater evidence of mutagenicity, with a weak positive response in mammalian cells in culture. It also induces cell transformation in mammalian cells in culture.

IV. REFERENCES

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O'Donoghue, JL, Haworth, SR, Curren, RD, et al. 1988. Mutagenicity studies on ketone solvents: Methyl ethyl ketone, methyl isobutyl ketone, and isophorone. Mutat. Res. 206: 149-161.

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